

RECEIVED
JAN 12 2004
TECH CENTER 1600/2900

THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Elizabeth M. Denholm, Elizabeth Cauchon, and Paul J. Silver

Serial No.: 09/727,873

Group Art Unit: 1651

Filed: December 1, 2000

Examiner: M. Meller

For: *ATTENUATION OF FIBROBLAST PROLIFERATION*

Assistant Commissioner for Patents
Washington, D.C. 20231

APPEAL BRIEF

Sir:

This is an appeal of the final rejection of claims 1-11 in the Office Action mailed March 27, 2002, maintained in the Advisory Action mailed July 17, 2002, in the above-identified patent application. A Notice of Appeal was filed on August 28, 2002. Submitted with this Appeal Brief is a Petition for Extension of Time for one month, along with the required \$55.00 fee for a small entity, to extend the period for filing the appeal brief to and including November 28, 2002. A check in the amount of \$160.00 for the filing of this Appeal Brief by a small entity is also enclosed.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, IBEX Technologies Inc., a corporation of Canada, having its principal place of business at 5485 Pare, Montral, Quebec, H4P 1P7 Canada, and its successor in interest, BioMarin Pharmaceuticals Inc., Novato, CA.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 1-11 are pending. Claims 1-11 are on appeal. The text of each claim on appeal, as amended, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in the Amendment faxed June 28, 2002. The amendment will be entered according to the Advisory Action mailed July 16, 2002. A copy of amended claims as pending is attached as Appendix to this Appeal Brief.

(5) SUMMARY OF THE INVENTION

The claims are drawn to the use of an effective amount of a specific glycosaminoglycan degrading enzyme, either a dermatan sulfate or chondroitin sulfate degrading enzyme, to treat fibroproliferative diseases (p. 6, lines 20-25) by reducing the size of a fibrous tissue in a patient by decreasing fibrous cell proliferative response to growth factors or reducing secretion of collagen by fibroblasts. The applicants used these specific glycosaminoglycan degrading enzymes to remove dermatan sulfate and chondroitin sulfate, which include chondroitin sulfate B, and to a lesser extent, chondroitin sulfate A or C, from cell surfaces (p. 6, lines 20-22). The enzymatic removal of chondroitin sulfate B, and A or C effectively decreases growth factor receptors on the cells and thereby decreases the cell proliferative response to such growth factors

(p. 8, lines 24-27; p. 11, lines 25-28). In addition, removal of chondroitin sulfates reduces secretion of collagen, one of the major extracellular matrix components (p. 8, lines 24-27) of a fibrous tissue. Through the combined inhibition of fibroblast proliferation and collagen synthesis, treatment with a glycosaminoglycan degrading enzyme such as chondroitinase B or chondroitinase AC decreases the size of fibrous tissue found in psoriasis, scleroderma, keloids and surgical adhesions (p. 11, line 25 to p. 12, line 2).

Example 1 demonstrates the specificity of the highly purified chondroitinase B and chondroitinase AC, respectively. The highly purified chondroitinase B has a relative specificity for chondroitin sulfate B over chondroitin sulfates A or C of 100:0.01 and 100:0.01, respectively (p. 13, Table 1). Conversely, the highly purified chondroitinase AC has a relative specificity for chondroitin A or C over chondroitin sulfate B of 100:0.05 or 59:0.05, respectively (p. 13, Table 1). Examples 4 and 5 show that highly purified chondroitinase B and chondroitinase AC are effective in inhibiting cell proliferation (p. 16, line 10 to p. 17, line 6; Figures 5A and 5B) and collagen synthesis (p. 17, line 26 to p. 18, line 2; Figure 6). *In vivo* tests were performed as shown in Examples 6 and 7, demonstrating that highly purified chondroitinase b and chondroitinase are effective for inhibition of fibroblast proliferation and for treating fibrosis in mouse.

Formulations for various local or systemic administrations are disclosed. The composition can be administered via, for example, topical application or injection (p. 9, line 1 to p. 10, line 20). Chondroitinase B or chondroitinase AC can be also administered in combination with other therapeutic agents such as antibiotics, antibodies to cytokines and chemokines, anti-

inflammatories such as cortisone, or other useful agents apparent to those skilled in the art (p. 10, lines 21-26).

(6) ISSUE ON APPEAL

The issue presented on appeal is whether claims 1-11 are obvious under 35 U.S.C. § 103(a) over U.S. Patent No. 6,153,187 to Yacoby-Zeevi ("Yacoby-Zeevi") in view of U.S. Patent No. 5,985,582 to Triscott ("Triscott").

(7) GROUPING OF CLAIMS

The claims do not stand or fall together, as discussed below. Prior art allegedly generally relating to the method of claim 1 in general does not disclose the method of claims 2, 3, 4, or 5 which are drawn to a specific dermatan sulfate or chondroitin sulfate degrading enzyme defined therein. Prior art allegedly generally relating to the method of claim 1 does not disclose the subject matter of claims 6, 7 or 8 which are drawn to treatment of a specific disorder which may be a skin disorder such as scleroderma or psoriasis or keloid scarring or pulmonary fibrosis. Prior art which allegedly generally relates to the method of claim 1 does not disclose the specific method of claims 9, 10 or 11 which further provides that the enzyme is administered systemically, administered topically or locally at or adjacent to a site in need of treatment, or administered in a controlled and/or sustained release formulation.

(8) ARGUMENTS

(a) The Claimed Method Provides An Effective Way for Decreasing Fibrous Tissue Size Which Is Lacking in the Prior Art

Claim 1 is drawn to a method to decrease fibrous tissue size by administering to an

individual in need of treatment **an effective amount** of a dermatan sulfate or chondroitin sulfate degrading enzyme to decrease fibrous cell proliferative response to growth factors, reduce secretion of collagen by fibroblasts, and thereby decrease the size of fibrous tissue.

The dependent claims add further limitations:

The method is further limited to a method using a bacterial dermatan or chondroitin sulfate degrading enzyme isolated from any of the bacteria defined therein (claim 2), mammalian enzyme (claim 3), bacterial enzyme (claim 4), and chondroitinase B (claim 5). The method of claim 1 is also limited by the disorder to be treated, e.g., skin disorder (claim 6) which may be, among others, scleroderma or psoriasis (claim 7), keloid scarring or being at risk of keloid scarring, or pulmonary fibrosis (claim 8). The method of claim 1 is further limited by the mode of administration, e.g., systemic administration (claim 9), topical or local administration at or adjacent to a site in need of treatment (claim 10), or administration in a controlled and/or sustained release formulation (claim 11).

Glycosaminoglycans, including chondroitin sulfates A, B or C, dermatan and heparan sulfates, are the sulfated polysaccharide components of proteoglycans located on cell surfaces, where they act as co-receptors for cytokines and growth factors and in the extracellular space where they form the structure of the extracellular matrix and serve as a supporting and organizational structure of tissues and organs (p. 6, lines 8-13). Studies on glycosaminoglycans were largely carried out using a single enzyme chondroitinase ABC, which degrades all three chondroitin sulfates A, B, and C, (see Lyon, et al. (1998) J. Biol. Chem. 273:271-278; Maeda, et al. (1996) J. Biol. Chem. 271:21446-21452; Milev, et al. (1998) J. Biol. Chem. 273:21439-

21442; Rapraeger, 1989, and Schmidt, et al. (1992) J. Biol. Chem. 267:19242-19247), isolated from *Proteus vulgaris* (Yamagata, et al. (1968) J. Biol. Chem. 243:1523-1535), all cited in the Information Disclosure Statement. Prior to the development of the methods disclosed herein, there was no disclosure of using a glycosaminoglycan degrading enzyme such as chondroitinase B and chondroitinase AC to (1) decrease fibrous cell proliferative response to growth factors, and (2) reduce secretion of collagen by fibroblasts, so as to decrease the size of a fibrous tissue (p. 2, lines 10-19; Figures 6-9).

The success of the claimed method is evident. As shown in Figure 7, after skin sections were treated with 1 and 10 IU/ml of chondroitinase B for 8 days, cell proliferation was inhibited by 35% and 48% respectively, in skin treated with 1.0 and 10 IU/ml of chondroitinase B (p. 19, lines 12-15). The amount of mRNA was found to be significantly less for both procollagen type I and for the collagen synthesis promoting cytokine, TGF β in lungs of mice treated with chondroitinase B (p. 21, lines 1-9).

The enzymes useful in the claimed method include, for example, heparinase 1 from *Flavobacterium hparinum*, heparinase 2 from *Flavobacterium hparinum*, heparinase 3 from *Flavobacterium hparinum*, chondroitinase AC from *Flavobacterium hparinum*, and chondroitinase B from *Flavobacterium hparinum*, heparinase from *Bacteroides* strains, heparinase from *Flavobacterium* Hp206, heparinase from *Cytophagia* species, chondroitin sulfate degrading enzymes from *Proteus vulgaris*, chondroitin sulfate degrading enzymes from *Microcossus*, chondroitin sulfate degrading enzymes from *Vibrio* speices, chondroitin sulfate degrading enzymes from *Arthrobacter aurescens*, these enzymes expressed from recombinant

nucleotide sequences in bacteria and combinations thereof (p. 7, lines 12-23). Other useful enzymes can be isolated from mammalian cells, which include heparanases, arylsulfatase B, N-acetylgalactosamine-6-sulfatase, and iduronate sulfatase (p. 7, lines 23-25).

The enzymes can be formulated into various formulations for both local and systemic administration (p. 9, line 16), e.g., injection, parenteral, intradermal, subcutaneous, or topical application, or internal topical applications (p. 9, line 2 to p. 10, line 20). The formulation may include other therapeutic agents such as antibiotics, antibodies to cytokines and chemokines which include, e.g., TNFalpha, TGFbeta, I1-1, and I1-6, and anti-inflammatories such as cortisone (p. 10, lines 22-26).

As discussed below, the prior art provides no guidance to providing an effective amount of dermatan sulfate or chondroitin sulfate degrading enzyme to (1) decrease fibrous cell proliferative response to growth factors, and (2) reduce secretion of collagen by fibroblasts. Moreover, the prior art fails to recognize the need to decrease the size of a fibrous tissue. Therefore the prior art not only fails to disclose or make obvious the subject matter of the independent claims, but also fails to disclose or make obvious the subject matter of the dependent claims.

(b) Rejections under 35 U.S.C. §103

Claims 1-11 were rejected as obvious over U.S. Patent No. 6,153,187 to Yacoby-Zeevi ("Yacoby-Zeevi") in combination with U.S. Patent No. 5,985,582 to Triscott ("Triscott").

1. The cited Art

U.S. patent No. 6,153,187 to Yacoby-Zeevi

Yacoby-Zeevi describes using glycosaminoglycan degrading enzymes for treating pulmonary disease characterized by an accumulation of mucoid, mucopurulent or purulent material (col. 1, lines 15-19) by reducing the viscosity of the mucoid material (col. 9, lines 50-61; col. 10, lines 9-21). The disorder that Yacoby-Zeevi is referring to is cystic fibrosis (see col. 1, line 29 to col. 4, line 32; col. 6, lines 30 to 62). Although there is an attempt to broaden the disorders to be treated (col. 8, lines 13-21), these are still all characterized by "an accumulation of mucoid, mucopurulent or purulent material", and the amount of glycosaminoglycan degrading enzyme that is administered is that amount which decreases the viscosity of the material (see col. 7, lines 42-49 and col. 8, lines 22-26).

In particular, Yacoby-Zeevi teaches using a glycosaminoglycan degrading enzyme for thinning, liquefying and reducing adhesivity of viscous airway secretions associated with respiratory diseases and sinusitis (col. 9, lines 50-59). The enzymes are used to reduce at least one of the following: the visco-elasticity of the material in a patient's airway, pathogens infectivity and inflammation (col. 10, lines 10-20). Yacoby-Zeevi addresses the use of aerosolized enzymes to treat the accumulation of very thick sputum found in cystic fibrosis (Id.). The glycosaminoglycan degrading enzymes include endoglycosidases such as mammal heparanase and connective tissue activating peptide III; heparinase I, II, and III, heparinase T-I, T-II, T-III and T-VI from *Bacillus circulans*; β -glucuronidase; Controitinase ABC, and chondroitinase B and C (col. 5, lines 18-37).

U.S. patent No. 5,985,582 to Triscott ("Triscott")

Triscott describes an assay of antithrombin in plasma using an modified heparin compound (col. 5, lines 60-63). An enzyme can be used to cleave one or more disaccharides from heparin to form the modified heparin (col. 6, lines 31-34). The enzyme can be chondroitinase CAI, chondroitinase B, chondroitinase C, or chondroitinase AC (col. 6, lines 34-42). No therapeutic uses for treating patients for any disease are suggested nor mentioned. Triscott describes chondroitinase B for making a modified heparin useful in an "improved thrombin-based ATIII assay" (col. 7, lines 55-65).

The combination of Yacoby-Zeevi with Triscott

Yacoby-Zeevi teaches using a glycosaminoglycan degrading enzyme to degrade the glycosaminoglycans in secretions blocking the airways of patients having diseases such as cystic fibrosis (CF) (col. 7, lines 45-49; col. 10, lines 10-13). Triscott teaches using chondroitinase B to modify heparin to make a heparin derivative useful in an antithrombin assay.

2. The Legal standard under 35 U.S.C. § 103(a)

In making an obviousness rejection under 35 U.S.C. § 103(a), the examiner has the burden under 35 U.S.C. § 103 to establish a *prima facie* case of obviousness. *In re Warner et al.*, 379 F.2d 1011, 154 U.S.P.Q. 173, 177 (C.C.P.A. 1967); *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598-99 (Fed. Cir. 1988). To establish a *prima facie* case of obviousness, the examiner must first establish that all the claim limitations are taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974); *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (CCPA 1970). If the examiner has met his burden of establishing that the

cited art discloses all the claim limitations, the Examiner still has the burden to prove that there is some suggestion or motivation to modify the references or to combine the teachings of the reference as appellants have done. *In re Dow Chem. Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Such a motivation **cannot** be based on the knowledge provided by the Appellant's disclosure. *In re McLaughlin*, 443 F.2d 1392, 1395 (CCPA 1971); *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988) (while the cited references disclosed each element of the claims in dispute, the Court nevertheless held that such a combination was improper because the cited references lack some **objective teachings** to combine the references)).

The examiner must also show that there is a reasonable expectation of success. *In re Dow Chem. Co.*, 837 F.2d 469. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on the Appellant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Geiger*, 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987); *In re Lalu and Foulletier*, 747 F.2d 703, 705, 223 U.S.P.Q. 1257, 1258 (Fed. Cir. 1984). Claims for an invention are not *prima facie* obvious if the primary references do not suggest all elements of the claimed invention and the prior art does not suggest the modifications that would bring the primary references into conformity with the application claims. *In re Fritch*, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992); *In re Laskowski*, 871 F.2d 115 (Fed. Cir. 1989).

3. Claims 1-11 are not obvious over the cited art

The cited references individually do not make claims 1-11 prima facie obvious

Claims 1-11 are not obvious over the cited art. First, none of the prior art references individually disclose every element of the claimed method, which recites: administering to an individual in need of treatment **an effective amount** of a dermatan sulfate or chondroitin sulfate degrading enzyme to **(1) decrease fibrous cell proliferative response to growth factors, and (2) reduce secretion of collagen by fibroblasts** to decrease the size of fibrous tissue. Nor does any one of the cited references provide motivation for one of ordinary skill in the art to modify any of the cited references to arrive at the method defined in any of claims 1-11.

As discussed above, Yacoby-Zeevi teaches using a glycosaminoglycan degrading enzyme, which include chondroitinase ABC and chondroitinase B and C, for thinning, liquefying and reducing adhesivity of viscous airway secretions associated with respiratory diseases and sinusitis (col. 9, lines 50-59). The enzymes are used to reduce at least one of the following: the visco-elasticity of the material in a patient's airway, pathogens infectivity and inflammation (col. 10, lines 10-20). Therefore, Yacoby-Zeevi does not teach or provide the motivation for one of ordinary skill in the art to decrease the size of fibrous tissue by administering to an individual in need of treatment an effective amount of a dermatan sulfate or chondroitin sulfate degrading enzyme to (1) decrease fibrous cell proliferative response to growth factors, and (2) reduce secretion of collagen by fibroblasts.

The Examiner asserted that, because Yacoby-Zeevi teaches treating cystic fibrosis, Yacoby-Zeevi thereby teaches decreasing the size of fibrous tissue. This assertion is unfounded.

Cystic fibrosis is characterized by abnormally thick, sticky mucus due to the faulty transport of sodium and chloride (salt) within cells lining organs such as the lungs and pancreas, to their outer surfaces. Therefore, Yacoby-Zeevi describes a method of treating cystic fibrosis using the glycosaminoglycan degrading enzymes to **reduce the abnormally thick, sticky mucus** (col. 9, lines 55-60).

In contrast, to reduce the size of a fibrous tissue, one would need to control and reduce the growth of the fibrous tissue. The claimed method achieves this goal by administering to an individual in need of treatment **an effective amount** of a dermatan sulfate or chondroitin sulfate degrading enzyme to (1) decrease fibrous cell proliferative response to growth factors, and (2) reduce secretion of collagen by fibroblasts. Therefore, Yacoby-Zeevi fails to teach or provide a motivation for one of ordinary skill in the art to arrive at the claimed method. Moreover, because Yacoby-Zeevi only teaches reducing the thick and sticky mucus in the airway of the patients of a respiratory disease, Yacoby-Zeevi would not lead one of ordinary skill in the art to have a reasonable expectation of success of the claimed method, which is drawn to the reduction of a fibrous tissue in an individual. *See In re Fritch*, 23 U.S.P.Q.2d 1780; *see also In re Laskowski*, 871 F.2d 115. As such, Yacoby-Zeevi does not render claims 1-11 *prima facie* obvious under 35 U.S.C. § 103.

Nor does Triscott make *prima facie* obvious claims 1-11. As shown in the foregoing discussion, Triscott teaches using a chondroitinase, which includes chondroitinase AC and chondroitinase B to modify heparin for use in **an antithrombin assay**. Triscott, therefore, is irrelevant to the claimed method, which requires administering to an individual an effective

amount of a dermatan or chondroitin sulfate degrading enzyme to (1) decrease fibrous cell proliferative response to growth factors, and (2) reduce secretion of collagen by fibroblasts so as to reduce the size of a fibrous tissue.

The cited references in combination do not make claims 1-11 prima facie obvious

The cited references in combination do not teach the claimed method. As discussed above, any teaching of Yacoby-Zeevi and Triscott combined would be using a chondroitin sulfate degrading enzyme to reduce the thick and sticky mucus in the airway of a patient having a respiratory disease, which is different from using a dermatan or chondroitin sulfate degrading enzyme in an individual in need of treatment to decrease the size of a fibrous tissue. Yacoby-Zeevi and Triscott, therefore, fail to teach or provide the motivation for one of ordinary skill in the art to arrive at the claimed method. Further, because Yacoby-Zeevi and Triscott only teach using a chondroitin sulfate degrading enzyme to reduce the mucus in the airways of a patient having a respiratory disease, Yacoby-Zeevi and Triscott, in combination, would not lead one of ordinary skill in the art to a reasonable expectation of the claimed method, which is drawn to administering to an individual **an effective amount** of a dermatan or chondroitin sulfate degrading enzyme to reduce the size of a fibrous tissue. Therefore, Yacoby-Zeevi and Triscott, in combination, do not make claims 1-11 *prima facie* under 35 U.S.C. § 103. *See In re Fritch*, 23 U.S.P.Q.2d 1780; *see also In re Laskowski*, 871 F.2d 115.

4. The Examiner has failed to examine the dependent claims

The enzymes defined by the dependent claims 2-5 have different properties, especially between those enzymes obtained from a mammalian source versus those enzymes obtained from

a bacterial source. The enzymes differ in substrate specificity as well as specific activity. The prior art Triscott teaches a bacterial chondroitinase B from a bacteria only for use on an isolated polysaccharide for use in a diagnostic assay - there is no teaching that it would be effective *in vivo* on mammalian *cells*. There is nothing leading one skilled in the art to even try the enzyme on mammalian cells as a therapeutic. Yacoby-Zeevi provides no guidance at all as to the source of the enzymes or the effective amounts or that they would have any effect on mammalian *cells*. See col. 11, lines 34-40. The only enzyme for which any adequate details are provided is a human heparanase (col. 11, lines 46-5). It is well known that the substrate specificity of a mammalian heparanase is completely different from that of a bacterial heparinase, and that a human heparanase is not a dermatan sulfate or chondroitin sulfate degrading enzyme as required by the claims.

None of the prior art even mentions treatment of skin disorders (claim 6), much less scleroderma or psoriasis (claim 7) or keloid scarring (claim 8).

No art has been cited for topical administration (claim 10) or for controlled or sustained release formulations (claim 11).

(9) SUMMARY

The claimed methods are not anticipated by or obvious from the prior art cited by the examiner, alone or in combination. The prior art fails to disclose the claimed elements, the motivation to combine, and any expectation of success. The examiner has failed to examine the dependent claims, but grouped them together with the independent claim 1. The examiner has failed to recognize the importance of the limitation of "an effective amount" "to decrease fibrous

cell proliferative response to growth factors, reduce secretion of collagen (note, this is not of glycosaminoglycan secretions, as in the case of cystic fibrosis), and thereby reduce the size of fibrous tissue.

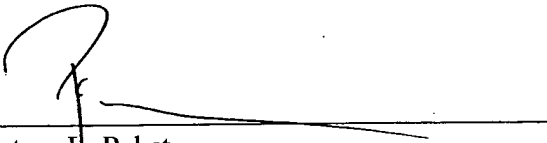
The only art cited by the examiner discloses either the use of a single bacterial enzyme to degrade an isolated polysaccharide for use in a diagnostic assay or the use of a human heparanase (which is not within the claimed classes or species of enzymes) to reduce the viscosity of glycosaminoglycan secretions. Nowhere is there any teaching that dermatan sulfate or chondroitin sulfate degrading enzymes would have any effect on fibrous cells, much less what an effective dosage would be.

Accordingly, the prior art fails to disclose the claimed elements, the motivation to combine into a method as appellants have done, nor any teaching of how to combine as appellants have done so that there is even a remote chance of success.

(10) CONCLUSION

Allowance of all claims 1-6, 8-12 and 14-24 is earnestly solicited.


Respectfully submitted,


Patrea L. Pabst
Reg. No. 31,284

Date: November 27, 2002
Holland & Knight LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, GA 30309-3400
(404) 817 - 8473
(404) 817 - 8588 (fax)

Certificate of Mailing Under 37 CFR § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to BOX AF, Assistant Commissioner for Patents, Washington, D.C. 20231.


Patrea L. Pabst

Date: November 27, 2002

TABLE OF CONTENTS

(1)	REAL PARTY IN INTEREST
(2)	RELATED APPEALS AND INTERFERENCES
(3)	STATUS OF CLAIMS ON APPEAL
(4)	STATUS OF AMENDMENTS
(5)	SUMMARY OF THE INVENTION
(6)	ISSUE ON APPEAL
(7)	GROUPING OF CLAIMS
(8)	ARGUMENTS
(a)	The Claimed Method Provides An Effective Way for Decreasing Fibrous Tissue Size Which Is Lacking in the Prior Art
(b)	Rejections under 35 U.S.C. §103
1.	The cited art
2.	The Legal standard under 35 U.S.C. § 103(a)
3.	Claims 1-11 are not obvious over the cited art
4.	The examiner has failed to examine the dependent claims
(9)	SUMMARY
(10)	CONCLUSION
	Certificate of Mailing
	Appendix: Claims on Appeal
	Table of Contents

Appendix: Claims on Appeal

1. (twice amended) A method to decrease fibrous tissue size comprising administering to an individual in need of treatment thereof an effective amount of a dermatan sulfate or chondroitin sulfate degrading enzyme to decrease fibrous cell proliferative response to growth factors, reduce secretion of collagen by fibroblasts, and thereby decrease the size of fibrous tissue.
2. The method of claim 1 wherein the enzyme is selected from the group consisting of bacterial dermatan or chondroitin sulfate degrading enzyme and is selected from the group consisting of chondroitinase AC from *Flavobacterium heparinum*, chondroitinase B from *Flavobacterium heparinum*, chondroitin sulfate degrading enzymes from *Bacteroides* species, chondroitin sulfate degrading enzymes from *Proteus vulgaris*, chondroitin sulfate degrading enzymes from *Micrococcus*, chondroitin sulfate degrading enzymes from *Vibrio* species, chondroitin sulfate degrading enzymes from *Arthrobacter aurescens*, arylsulfatase B, N-acetylgalactosamine-6-sulfatase and iduronate sulfatase from mammalian cells, these enzymes expressed from recombinant nucleotide sequences in bacteria and combinations thereof.
3. The method of claim 1 wherein the enzyme is a mammalian enzyme.
4. The method of claim 1 wherein the enzyme is a bacterial enzyme.
5. The method of claim 4 wherein the chondroitinase is chondroitinase B.
6. The method of claim 1 wherein the individual has a skin disorder.
7. The method of claim 6 wherein the skin disorder is scleroderma or psoriasis.
8. The method of claim 1 wherein the individual has keloid scarring or is at risk of

keloid scarring, or has pulmonary fibrosis.

9. The method of claim 1 wherein the enzyme is administered systemically.

10. The method of claim 1 wherein the enzyme is administered topically or locally at or adjacent to a site in need of treatment.

11. The method of claim 1 wherein the enzyme is administered in a controlled and/or sustained release formulation.

ATL1 #554208 v1